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CLINICAL REVIEW

Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies

Chiara Baglioni [a,*], Wolfram Regen [a], Armand Teghen [a], Kai Spiegelhalder [a,b], Bernd Feige [a], Christoph Nissen [a], Dieter Riemann [a]

[a] Department of Psychiatry and Psychotherapy, University of Freiburg Medical Center, Hauptstraße 5, 79104 Freiburg, Germany
[b] Freiburg Institute for Advanced Studies (FRIAS), University of Freiburg, Albertstraße 19, 79104 Freiburg, Germany

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SUMMARY

Insomnia is a highly prevalent health problem worldwide. Primary insomnia (PI), i.e., insomnia not due to another disorder or substance use, represents a model to elucidate the pathophysiology of sleep. However, prior research in patients with PI has failed to demonstrate consistent abnormalities in the state-of-the-art assessment of sleep (polysomnography). The aim of this meta-analysis was to clarify whether there are identifiable polysomnographic sleep changes that correspond to the subjective complaints of patients with PI. Medline and PsycInfo databases were searched from 1994 to 2012. Effects were calculated as standardized mean differences. Studies were pooled with the random-effects meta-analytic model. Twenty-three studies met inclusion criteria. In total, 582 patients with PI and 485 good sleeper controls (GSC) were evaluated. The results showed that patients with PI present a disruption of sleep continuity and a significant reduction of slow wave sleep (SWS) and rapid eye movement (REM) sleep compared to GSC. The observed changes in sleep architecture, i.e., reductions in SWS and REM sleep, hitherto did not count among the typical polysomnographic findings in patients with PI. An advanced knowledge of the polysomnographic changes in PI may add to foster the understanding of the pathophysiology of sleep and its bi-directional relationships with somatic and mental disorders.

Introduction

Insomnia is defined as complaint of difficulties initiating/maintaining sleep or non-restorative sleep accompanied by decreased daytime functioning persisting for at least four weeks (DSM-IV[1]; DSM-IV-TR[2]). The current version of the DSM (DSM-IV-TR)[2] identifies two main categories of insomnia: 1) primary insomnia in which the condition of insomnia is not attributable to other medical or psychiatric disorders; and 2) secondary insomnia in which another medical or psychiatric disorder has to be identified as the primary cause. This dual interpretation has been strongly criticized and will be eliminated in the next edition of the DSM, the DSM-V.[3] The new definition will refer to "insomnia disorder" as the main diagnostic category for insomnia with respect to which clinically comorbid conditions (both medical and psychiatric) can be coded.

The identification of insomnia as an independent diagnostic entity has stimulated research about two main questions: what are the psychophysiological characteristics underlying the disorder of insomnia; and which are the psychophysiological characteristics explaining its high comorbidity with other clinical conditions Because the DSM-V has not yet been published, researchers have until now referred to the DSM-IV condition of primary insomnia – i.e., insomnia in the absence of other clinical conditions or substance abuse – as a useful research model to understand the pathophysiology of disrupted sleep. The condition of primary insomnia in the absence of other clinical disorders or substance abuse is consistent with the definition of insomnia disorder with no specified clinically comorbid conditions which will be adopted in the DSM-V. Accordingly, this condition has been the focus of the present study and will be indicated with the abbreviation "PI".

One of the main controversial results in the study of PI is whether it is associated with changes in sleep or not, based on the findings from many experimental studies which failed to demonstrate consistent electrophysiological correlates of the subjective complaints. However, these controversial findings may be related to different methods or definitions. For this reason, the aim of this meta-analysis was to analyze all studies in which the electrophysiological correlates of sleep were recorded with polysomnography (PSG) in patients with PI as compared to healthy good sleeper controls (GSC).

* Corresponding author. Tel.: +49 761 270 65890; fax: +49 761 270 66190.
E-mail address: chiara.baglioni@uniklinik-freiburg.de (C. Baglioni).

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Abbreviations

DSM-IV	diagnostic and statistical manual for mental disorders (4th edition)
DSM-IV-TR	diagnostic and statistical manual for mental disorders (4th edition, text revision)
DSM-V	diagnostic and statistical manual for mental disorders (5th edition)
EEG	electroencephalogram
EMG	electromyographam
EOG	electrooculogram
GSC	good sleeper controls
I^2	heterogeneity index
MDD	major depressive disorder
MOOSE	guidelines on meta-analysis of observational studies in epidemiology
NA	number of awakenings
OSA	obstructive sleep apnea
PI	the condition of primary insomnia in the absence of other clinical disorders or substance abuse (DSM-IV-TR)/the condition insomnia disorder with no specified clinically comorbid conditions (DSM-V)
PRISMA	guidelines for preferred reported items for systematic reviews and meta-analysis
PSA	power spectral analysis
PSG	polysomnography
PTSD	post-traumatic stress disorder
REM	rapid eye movement
REML	REM latency
RLS	restless legs syndrome
S1	duration of stage 1
S2	duration of stage 2
SEI	sleep efficiency index
SMI	sleep maintenance insomnia
SOL	sleep onset latency
SWS	duration of slow wave sleep
TIB	total time in bed
TST	total sleep time
WASO	wake after sleep onset

In the following paragraphs of the introduction, a brief overview of insomnia in terms of its prevalence and costs will be presented and the history of the change in the conceptualization from symptom to disorder will be discussed. Then, the assessment of the symptoms will be described, and finally, the focus will be specifically on studies evaluating electrophysiological sleep recordings in PI.

Insomnia: prevalence, costs and change of conceptualization

Chronic insomnia afflicts about 10% of the population in western industrialized countries[4] with women being more frequently affected than men[5] and an increasing prevalence with older age.[4] More than 70% of subjects experiencing insomnia today will still suffer from it the next year as the disorder tends to take a chronic course.[6] PI occurs in about 2–4% of the adult population.[4] Recent research has emphasized the economical and societal costs of insomnia. For example, in the US, the costs of insomnia due to low work performance and absenteeism have been estimated to exceed 60 billion $ per year.[7] Additionally, the condition of insomnia is associated with increased healthcare utilization and indirect costs, for example linked with a higher rate of accidents (e.g.,[8]).

The classic psychiatric view has conceptualized insomnia as a symptom of an underlying mental disorder, with affective disorders being the most important ones. This conceptualization has been substantially challenged based both on clinical observations and experimental findings showing that, at least with respect to major depression, insomnia often precedes it and it does not remit after successful treatment of depression (e.g.,[9]). In addition, a recent meta-analysis found insomnia to be an independent clinical predictor of major depression.[10] Symptoms of insomnia are a pervasive problem not only for patients with depression, but also for patients with bipolar disorders, anxiety disorders, alcoholism, eating disorder, and schizophrenia.[11–13] Recent theories have proposed that insomnia may be involved in the causation and the maintenance of psychiatric disorders by representing a transdiagnostic mechanism.[14] Consistently, sleep-related processes play an important role for healthy emotional and cognitive functioning.[15] Moreover, recent evidence has shown that insomnia, and specifically PI, is also associated with emotional alterations (for a review see[16]). However, PI is not the same as sleep deprivation, as it involves adaptation processes and, as mentioned above, it has not been ascertained that it is associated with alterations of sleep physiology. The understanding of if and which physiological sleep changes are associated with PI should help in clarifying its association with emotional processes and psychopathology.

The assessment of insomnia

The sleep complaint in patients with insomnia can be evaluated through technical assessment or by subjective self-monitoring. The gold standard of technical sleep assessment is polysomnography (PSG) including electrophysiological recordings of brain activity (EEG), muscle activity (EMG), and eye movements (EOG). The recording is scored and categorized into different stages – wake; sleep stage 1; sleep stage 2; slow wave sleep; rapid eye movement (REM) sleep – and typically PSG-derived sleep parameters are grouped into sleep continuity variables (e.g., sleep onset latency (SOL), number of awakenings), sleep architecture variables (e.g., duration of each sleep stage in minutes and %) and REM sleep variables (i.e., REM latency, REM density).

Subjective self-monitoring of sleep is generally achieved by sleep diaries, asking subjects to provide an estimate of sleep-related variables (SOL, WASO, TST, etc.) every morning. Additionally, subjects are asked to document their daytime behaviors (e.g., medication or alcohol intake) in the evening.[17]

As insomnia is defined as complaint of poor sleep, its assessment is based primarily on subjective description of the symptoms, and not necessarily on pathological polysomnographic recordings. The international classification of sleep disorders (ICSD-2),[18] for example, identifies a type of insomnia, called paradoxical insomnia, characterized by a profound subjective complaint of poor sleep in the absence of polysomnographic alterations (total sleep time $\geq$ 6.5 h and a sleep efficiency $\geq$ 85%). In general, PSG recordings, allowing conventional sleep staging referring to standard criteria,[19,20] are not required for the clinical assessment of insomnia (e.g., consensus reports[21,22]).

PSG alterations in PI

While potential PSG alterations associated with insomnia play a secondary role in clinical settings, they are of high relevance in

order to describe the pathophysiology of the disorder. As mentioned above, research has focused on PI as a useful research model. Current pathophysiological models agree that the main etiological factor in the onset and the maintenance of PI is cognitive, emotional and physiological hyperarousal which is present during night and daytime (e.g.,[23]; for review, please refer to[24–27]). If people with PI are characterized by increased psychophysiological arousal, it is reasonable to assume that this should be associated with alterations of sleep continuity and architecture, such as lighter and less deep sleep. However, PSG impairment of sleep in PI is still a matter of controversy. Several studies applying PSG in patients with PI failed to find significant differences to GSC[28,29] or found only a modest impairment in the patient group.[30–33] Accordingly, many authors have criticized the use of PSG data to evaluate the clinical impairment of patients with PI. It can be speculated that contradictory results found in studies using PSG depend on different methods or definitions of insomnia. In addition, some authors have suggested the use of alternative EEG analyses, as for example, power spectral analysis (PSA) which is a method for quantifying the EEG's constituting frequency components including those that reflect the general arousal level of the brain.[34–36]

To our knowledge, the only previous quantitative summary of the literature on PSG data in patients with insomnia was provided by Benca et al.[37] In this meta-analysis, the authors analyzed all studies measuring sleep polysomnographically in psychiatric disorders, including insomnia.[37] This was an extensive study; however, as it was published 20 years ago, it had some limitations which might have influenced the results. First, the sleep variables were taken from either one night or from the average of all recorded nights. As a consequence, no attempt was made to eliminate the possible confounding influence of the "first night effect", which is the tendency of individuals to sleep worse during the first night of PSG,[38] or the "reverse first night effect", which may be encountered in patients with PI who have been reported to sleep better in the first laboratory night.[39] Second, no attempt was undertaken to avoid a possible overlap between subjects published repeatedly in different publications. Third, the definition of sleep variables was not taken into consideration as a source of bias. Fourth, considering the meta-analytic calculations, all studies were entered into the analysis with equal weight. Today, state-of-the-art software is available which automatically weights studies for sample size. Additionally, effect sizes and mean differences can be calculated in order to estimate the clinical importance of the findings. Last, with specific relation to the analyses of insomnia studies, no DSM-IV[1] definition of primary insomnia was available in 1992. Consequently, insomnia was defined either based on PSG abnormalities or on self-reported sleep patterns with no consideration of the daytime symptoms. This variability could of course, have had a strong impact on the results. Moreover, the authors did not focus specifically on PI, which may imply that the results could have been biased by comorbidity with other disorders.

Aim of the present meta-analysis

In the present study, we aimed to quantitatively summarizing all the data published so far in which conventional PSG was measured in patients with PI and in GSC. The objective was to describe the sleep profile of patients with PI and to identify future avenues for research.

Method

The meta-analysis was performed according to MOOSE[40] and PRISMA[41] guidelines. The first and second authors independently conducted the literature search and screened the titles and abstracts of potentially eligible studies. The first and the third author examined the full texts and collaborated to extract the data for the analyses.

Study selection

Search method for the identification of the studies

Studies evaluating PSG sleep in people with PI published in English, German, Italian, Spanish or French were identified via a literature search using PubMed and PsycInfo. The databases were searched from January 1994 through July 2012. 1994 was taken as the starting point, as in this year the DSM-IV[1] was published and studies could refer to this definition of primary insomnia. The key search terms included: "insomnia" linked to "polysomnogr*" or "sleep recordings" or "sleep stages" or "sleep architecture". The terms were searched as keywords, capturing the titles and abstracts. Further studies were added by examining the reference lists of identified papers. Unpublished studies were not included.

Screening of titles and abstracts

The exclusion criteria considered in the first screening of titles and abstracts were the following:

1) Studies focusing on other disorders than insomnia.
2) Studies published in languages different from English, German, Italian, Spanish or French.
3) Reviews, guidelines, statements, or comments.
4) Single case reports.
5) Animal studies.
6) Epidemiological studies in the general population.
7) Studies in which it was clearly stated in the abstract that a) no PSG recordings were used; b) no GSC group was investigated; or c) only one night of PSG was conducted. All other studies were selected for examination of the full text.

Selection of the full texts

After the initial screening of titles and abstracts, full texts were examined based on the exclusion criteria listed below. If necessary, corresponding authors were contacted for additional information (see Acknowledgements). The exclusion criteria at this stage were the following:

1) Diagnosis of insomnia not based on and not consistent with the DSM-IV[1] definition PI.
2) No group with the sole diagnosis of PI (e.g., group with mixed sleep disorders).
3) No drug wash-out for at least 1 week for all participants (or not specified).
4) No GSC group.
5) Only 1 PSG night was measured, or the PSG nights were not consecutive, or the analysis referred to the average of all nights measured including the first night, or the PSG data of night 2 were not available, or the PSG data were not reported in the text, or it was not specified to which PSG night the data referred.
6) No use of standard criteria to score sleep or not specified.
7) Too few information reported in the text and impossible to contact the author (e.g., no answer or e-mail address no longer valid).
8) No baseline data reported in a follow-up design.
9) The baseline (generally the 2nd) night of PSG was experimentally disturbed (e.g., blood sampling or skin temperature manipulations), unless it was specified that the procedure used did not disturb sleep.

10) Main text neither in English, German, Italian, Spanish, nor French.
11) Studies in which some participants overlap with the ones of an already included study.
12) No mean age of participants indicated.
13) PSG data for the GSC group not reported.

Data extraction

For each study, data on a number of procedural variables were collected in order to assess the quality of the studies. These variables included the sample size, socio-demographic and other methodological variables, and "blinding" of the sleep scoring. Socio-demographic and other methodological variables comprised sex, age, PSG night or nights to which the data referred and where the analyses were conducted (sleep clinic/laboratory/hospital vs. home). For age and sex, when detailed information was given only for one of the two groups, but it was reported that the other group was age- and sex-matched, the same mean/frequency values were used for all participants for qualitative analyses. In addition, when the age range was not specified, the mean age and the standard deviation were used to classify the study in a specific age range group. In order to compute meta-analytic parameters for continuous outcome variables, for each study, the means and the standard deviations of each sleep variable were collected in order to compute the mean between-group differences. Considering the variables indicating the duration of each sleep stage (stage 1; stage 2; slow wave sleep; REM sleep; and wake after sleep onset), percentages were preferred over minutes. However, when only minutes were reported, these were also included in the analysis. Specifically, for the following sleep variables we found a sufficient number of studies to conduct the meta-analytic computations: sleep efficiency index (SEI), SOL, TST, total time in bed (TIB), number of awakenings (NA), REM latency (REML), duration of stage 1 (S1), stage 2 (S2), slow wave sleep (SWS), REM sleep and WASO. Whenever reported, data derived from power spectral analyses and sleep diaries were collected and analyzed as well. When a study had more than one patient group of interest (e.g., one group with PI − psychophysiological type, and one group with PI − paradoxical type) we considered it twice as two different comparisons and divided the *N* of the control group by the number of patient groups of interest.

Meta-analytic calculations

All meta-analytic calculations were performed using the software "Comprehensive Meta-Analysis", version 2.[42] For each sleep variable, a separate meta-analysis was run. For each of these, effect sizes were calculated as standardized mean effect sizes (Cohen's *d*). The analyses were applied to the whole sample of studies which were pooled with the random-effects model, because of the considerable heterogeneity (different populations, different sleep recording procedures, etc.). In the random-effects model, it is assumed that the included studies differ systematically from each other. Accordingly, the effect sizes differ because of random errors within the studies, but also because of true variation in effect sizes between studies.

In order to test for heterogeneity, chi-squared tests and the I^2 statistic derived from the chi-squared values were used. I^2 is defined as the ratio of true heterogeneity to the total variation in the observed effects, where the total variation refers to the sum of the true variation (for example, due to differences in the methods between the studies) and the random error.[43] The higher the I^2 index, the higher the true variation within the studies and the need to identify sources of variability. Conventionally, an I^2 around 25% is taken as an indicator of low heterogeneity, an I^2 around 50% as an indicator of moderate heterogeneity, and an I^2 around 75% as an indicator of high heterogeneity. By contrast, an I^2 close to 0 may indicate that the total variation in the observed effects is too spurious, i.e., explained mainly by random error.

Possible sources of variability were evaluated through subgroup analyses. When possible, age, sex, definition of sleep variables, definition of PI, and duration of PI were analyzed as sources of heterogeneity. With respect to age, the studies were divided in two groups: adults ($\geq$18 and $\leq$60 y); mixed group of adults and elderly ($\geq$18 y). No study within our sample specifically evaluated young individuals ($<$18 y) or exclusively elderly ($\geq$60 y). With respect to sex, analyses were repeated by excluding studies in which all participants were males, in order to check whether some effects were specifically related to the number of men in the analyses. This procedure was chosen because almost all studies evaluated mixed samples of women and men; with only two studies including only male participants (see Table 1). No study of our sample evaluated exclusively women.

With respect to sleep variable definitions, studies were divided into groups depending on the definitions. That is, wherever it was possible, we grouped the studies for a consistent definition to check whether the variability in the calculation of some sleep variables could explain the heterogeneity (e.g., some studies defined sleep onset latency as the latency to stage 2 sleep, while other studies defined it as the latency to any sleep stage). In addition, the meta-analyses conducted on the whole sample of studies were repeated by excluding those studies in which PI was pre-defined based on PSG data. Finally, with respect to PI duration, a group of studies in which patients complained of the disorder on average for more than 5 y was selected and considered separately.

Prior to performing each meta-analytic computation for each sleep variable, we identified possible outliers in sensitivity analyses and excluded them from our study sample. For outlier identification, we followed a method suggested by Hedges and Olkin[44] based on the standardized residuals: studies with standardized residuals greater or equal to +3 and/or lower or equal to −3 were excluded from the analysis.

Results

Fig. 1 illustrates the search flow. Inserting the keywords, a total of 1227 abstracts were identified (768 abstracts in PubMed, 459 in PsycInfo). The screening of titles and abstracts led to 92 studies for which the full text was evaluated. The examination of the reference lists of the full texts identified 17 additional papers. The evaluation of the full texts led to a final sample of 23 studies. The 86 studies excluded and the reasons for the exclusion are listed in Table S1 (supplemental material online).

Table 1 lists the studies and the description of the study characteristics with respect to: a) definition of insomnia; b) type of PI; c) duration of PI; d) sample size; e) age; f) sex; g) past histories of mental disorders; h) PSG night(s) for data analysis; i) bedtime schedule; j) sleep diary data. Summarizing the included studies, 582 patients with PI (age 42.9 ± 8.9 y; 51.7% female) and 485 GSC (age 40.0 ± 8.1 y; 53.3% female) were evaluated by at least two nights of PSG recordings. Excluding the two studies focusing on males, the percentages of females is 56.4% in the group of patients with PI and 58.1% in the group of GSC. One study was considered twice as it included two groups of patients of interest, one with PI-psychophysiological type and one with PI-paradoxical type.[45] In all the included studies, sleep recordings were scored according to Rechtschaffen and Kales criteria.[19]

Quality of the studies

As mentioned above, the quality of the studies was assessed by using the following information: sample size; additional socio-

Table 1
Study characteristics.

Study characteristics	Definition of insomnia	Type of PI	Duration of PI	*N* (PI/GS)	Age	Sex	Past histories of mental disorders	PSG nights for data analyses	Bedtimes schedule	Sleep diary
Bastien et al., 2008[45,d]	DSM-IV (based on clinical interview, sleep diaries and questionnaires)	PI-psychophysiological type	9.4 ± 8.1 y	30 (15/7.5)	>18 and <60 y (23–52 y)	Mixed[e]	Not specified	2nd	Bedtime was determined according to reported bedtime on the sleep diary and PSG recordings had to be ≥8 h long	Yes – 2 weeks (TST; TWT; TIB; SEI)
Bastien et al., 2008[45,d]	DSM-IV (based on clinical interview, sleep diaries, questionnaires and PSG)	PI-paradoxical type	13.8 ± 9.7 y	30 (15/7.5)	>18 and <60 y (23–52 y)	Mixed[e]	Not specified	2nd	Bedtime was determined according to reported bedtime on the sleep diary and PSG recordings had to be ≥8 h long	Yes – 2 weeks (TST; TWT; TIB; SEI)
Bastien et al., 2003[46,d]	DSM-IV (based on clinical interview, sleep diaries and questionnaires)	PI (mixed difficulties 77%; *SMI* 10%; SOI 7%; EMI 7%)	24.6 ± 19.4 y	31 (15/16)	Mixed (≥55 y)	Mixed[e]	Not specified	Combined 2nd–3rd	Not specified (but Time in bed considered within the sleep variables – TIB considered)	Yes – 2 weeks (but only for screening)
Buysse et al., 2008[47]	DSM-IV (based on clinical interview and questionnaires)	PI	≥1 mo (based on DSM-IV criteria)	73 (48/25)	>18 and <60 y (mean age: PI: 30.8 ± 7.2; GS: 30.6 ± 7.4)	Mixed[e]	Excluded if in the last 6 months	2nd	Not specified (but TIB considered)	Yes – 1 week (TST; TIB; SEI; SOL; WASO) + post-sleep self-report after PSG nights
De Zambotti et al., 2011[48]	DSM-IV (based on clinical interview and questionnaires)	PI	≥1 mo (based on DSM-IV criteria)	16 (8/8)	>18 and <60 y (19–28 y)	Mixed[e]	Not specified	2nd	8 h	Yes (but only for screening)
Edinger et al., 2001[49]	DSM-IV (based on clinical interview and questionnaires)	PI (mixed difficulties 42.4%; *SMI* 42.4%; SOI 9.1%; poor sleep quality 6.1%)	9.5 ± 7.6 y	68 (33/35)	>18 and <60 y (mean ages: PI: 49.9 ± 5.8; GS: 46.5 ± 5.0)	Mixed[e]	Excluded	Combined 2nd–3rd	Participants were thoroughly interviewed to determine the customary bedtimes and rising times and asked to adhere to these times during the experiment period	No
Feige et al., 2008[50]	DSM-IV (based on clinical interview and questionnaires)	PI	≥1 mo (based on DSM-IV criteria)	200 (100/100)	Mixed (17–79 y)	Mixed[e]	Excluded	2nd	Scheduled for 8 h from 23:00 h to 07:00 h	Post-sleep self-report after PSG nights[f]
Ferri et al., 2009[51,d]	DSM-IV (based on subjective complaint)	PI	≥6 mo (based on ICSD-2 criteria)	32 (20/12)	>18 and <60 y (mean ages: PI: 48.2 ± 12.69; GS: 46.7 ± 15.21)	Mixed[e]	Excluded	2nd	Light-out time was based on individual habitual bedtime and ranged between 22:00 h and 23:00 h (and TIB considered)	No
Forget et al., 2011[52]	DSM-IV (based on clinical interview, sleep diaries and questionnaires)	PI (*SMI*)	16.1 ± 9.1 y	24 (12/12)	>18 and <60 y (26–56 y)	Mixed[e]	Not specified	3rd	Bedtime was fixed between 21:00 h and midnight and wake time was fixed between 05:00 and 08:00 h Participants were asked to stay in bed between 7 and 9 h and the usual sleeping schedule was accommodated as best as possible (±30 min)	Yes – 2 weeks (TST; SEI; SOL; WASO)

(*continued on next page*)

Table 1 (*continued*)

Study characteristics	Definition of insomnia	Type of PI	Duration of PI	*N* (PI/GS)	Age	Sex	Past histories of mental disorders	PSG nights for data analyses	Bedtimes schedule	Sleep diary
Hajak et al., 1995[53]	DSM-IV (based on clinical interview and PSG)	PI (including idiopathic insomnia -mainly *SMI*)	10.7 ± 7.9 y	15 (10/5)	>18 and <60 y (mean ages: PI: 41.3 ± 9.5; GS: 27.2 ± 0.7)	Mixed[e]	Excluded	2nd	The night session started at 17:00 h and finished at 08:00 h (and TIB considered)	No
Irwin et al., 2003[54,d]	DSM-IV (based on clinical interview and sleep diaries)	PI	≥1 mo (based on DSM-IV criteria)	48 (17/31)	>18 and <60 y (mean ages: PI: 49.8 ± 12.7; GS: 44.4 ± 11.4)	Males	4 PI patients fulfilled criteria for alcohol abuse (not dependence) in remission for greater than 6 months. Otherwise excluded	2nd	Lights out between 22:00 h and midnight	Yes − 2 weeks (but only for screening)
Jurysta et al., 2009[55]	DSM-IV + SEI <85% (based on PSG)	PI	≥1 mo (based on DSM-IV criteria)	28 (14/14)	Mixed (16–63 y)	Males	Not specified	3rd	Not specified (but TIB considered)	No
Lanfranchi et al., 2009[56]	DSM-IV (based on sleep diaries and questionnaires)	PI (mixed symptoms)	23 ± 10 y	26 (13/13)	>18 and <60 y (30–60 y)	Mixed[e]	Not specified	3rd	Not specified	Yes − 2 weeks (TST; SEI; SOL; WASO)
Lushington et al., 1999[57]	DSM-IV (based on clinical interview, sleep diaries and questionnaires)	PI (*SMI*)	≥6 mo (based on ICSD-2 criteria)	32 (16/16)	Mixed (≥55 y)	Mixed[e]	Not specified	Combined 3rd–4th	Not specified (but lights out time and TIB considered)	Yes − 1 week (but only for screening)
Merica et al., 1998[58,a]	DSM-IV (based on PSG)[a]	PI (including idiopathic insomnia − *SMI* or mixed symptoms)	≥6 mo (based on ICSD-2 criteria)	39 (20/19)	>18 and <60 y (20–47 y)	Mixed[e]	Not specified	2nd	Not specified	No
Niemcewicz et al., 2001[59,b]	DSM-IV (based on questionnaires)[b]	PI	6.4 ± 7 y	32 (16/16)	>18 and <60 y (21–55 y)	Mixed[e]	Not specified	2nd	Not specified	No
Parrino et al., 2009[60]	DSM-IV (based on clinical interview, sleep diaries, and PSG)	PI-paradoxical type	≥6 mo (based on ICSD-2 criteria)	40 (20/20)	>18 and <60 y (mean ages: PI: 45 ± 8; GS: 45 ± 8)	Mixed[e]	Not specified	2nd	Not specified	Post-sleep self-report after PSG nights[g]
Salin-Pascual et al., 2006[61,c]	DSM-IV[c]	PI	≥1 mo (based on DSM-IV criteria)	12 (6/6)	>18 and <60 y (mean ages: PI: 36.2 ± 11.7; GS: 26.5 ± 5.0)	Mixed[e]	Not specified	2nd	Not specified	No
Savard et al., 2003[62]	DSM-IV (based on clinical interview, sleep diaries and questionnaires)	PI (mixed difficulties 59%; *SMI* 6%; SOI 35%)	≥6 mo	36 (17/19)	>18 and <60 y (18–45 y)	Mixed[e]	Not specified	2nd	Not specified	Yes − 3 weeks (SEI)
Sforza and Haba-Rubio, 2006[63,d]	DSM-IV (based on clinical interview and sleep diaries)	PI (*SMI* 5; SOI 6; EMI 4)	≥6 mo	28 (15/13)	>18 and <60 y (mean ages: PI: 43.5 ± 9.4; GS: 40.2 ± 6.4)	Mixed[e]	Excluded	2nd	TIB was scheduled between 22:30 and 23:00 h and 07:00 h	Yes − 1 week (but only for screening) + post-sleep self-report after PSG nights (but used only to define good/bad quality of sleep nights)[g]
Siversten et al., 2009[64,d]	DSM-IV (based on sleep diaries and questionnaires)	PI	≥3 mo	90 (64/26)	Mixed (≥55 y)	Mixed[e]	Not specified	2nd	Not specified	Yes − 2 weeks (TST; SEI; SOL; WASO)

Staner et al., 2003[65,d]	DSM-IV (based on clinical interview and questionnaires)	PI	≥1 mo (based on DSM-IV criteria)	42 (21/21)	>18 and <60 y (mean ages: PI: 40.5 ± 10.3; GS: 44.3 ± 13.2)	Mixed[e]	Not specified	3rd	Not specified	No
Toussaint et al., 1995[38,d]	DSM-IV (based on clinical interview)	PI	≥1 mo (based on DSM-IV criteria)	88 (56/32)	>18 and <60 y (17–57 y)	Mixed[e]	Excluded	2nd	Patients were studied at their habitual sleep time but nevertheless within 22:00 h and midnight. Healthy volunteers were studied on entrained routine (22:00 h)	No
Vgontzas et al., 2002[66]	DSM-IV + SEI <80% (based on clinical interview and PSG)	PI	≥6 mo	22 (11/11)	>18 and <60 y (mean ages: PI: 31.6 ± 6.7; GS: 27.1 ± 6.4)	Mixed[e]	Not specified	Combined 2nd–3rd	The sleep schedule in the sleep laboratory was similar to the subjects' normal sleep schedule, which was between 22:00 and 23:00 h to 06:00 and 07:00 h	No

Abbreviations: DSM-IV, Diagnostic and statistical manual of mental disorders, fourth edition; EMI, early morning insomnia; GS, good sleepers; PI, patients with primary insomnia; PSG, polysomnography; SEI, sleep efficiency index; SMI, sleep maintenance insomnia; SOI, sleep onset insomnia; SOL, sleep onset latency; TIB, total time in bed; TST, total sleep time; TWT, total wake time; WASO, wake after sleep onset.

[a] Merica et al., 1998. The authors report that patients were diagnosed for either psychophysiological or idiopathic insomnia based on the ICSD-2. However, how this diagnosis was done is not reported (i.e., clinical interview or questionnaires). The identification of sleep maintenance insomnia or mixed symptoms was conducted through PSG.

[b] Niemcewicz et al., 2001. The authors report that patients were diagnosed for primary insomnia according the DSM-IV criteria. However, how the diagnosis was done is not reported. A number of screening questionnaires are reported in the text and PSG was performed after the diagnosis had already been done.

[c] Salin-Pascual et al., 2006. The authors report that patients were diagnosed for primary insomnia according the DSM-IV criteria. However, how the diagnosis was done is not reported (i.e., clinical interview or questionnaires).

[d] The following studies included other groups which were not considered in this meta-analysis. Specifically:

A. Bastien et al., 2008 – four groups: 15 individuals suffering from psychophysiological insomnia; 15 individuals with paradoxical insomnia; 12 individuals suffering from borderline personality disorder (BPD); and 15 self-defined good sleepers. The group with BPD was not considered.
B. Bastien et al., 2003 – three groups: 15 individuals suffering from psychophysiological insomnia; 15 individuals with insomnia and using benzodiazepine chronically; and 16 self-defined good sleepers. The group using benzodiazepine was not considered.
C. Ferri et al., 2009 – three groups: 20 patients with primary insomnia, 20 patients with restless legs syndrome (RLS), and 12 controls. The group with RLS was not considered.
D. Irwin et al., 2003 – three groups: 17 subjects with primary insomnia, 14 patients with major depression, and 31 controls. The group with major depression was not considered.
E. Sforza and Haba-Rubio, 2006 – three groups: 15 patients with primary insomnia, 45 patients with sleep-related breathing disorders (SRBD), and 13 controls. The group with SRBD was not considered.
F. Siversten et al., 2009 – three groups: 17 chronic zopiclone users, 64 drug-free patients with insomnia, and 26 controls. The group taking zopiclone was not considered.
G. Staner et al., 2003 – three groups: 21 patients with primary insomnia, 21 patients with major depression, and 21 controls. The group with major depression was not considered.
H. Toussaint et al., 1995 – three groups: 56 patients with primary insomnia, 38 patients with depression, and 32 controls. The group with depression was not considered.

[e] Mixed gender group of women and men.

[f] SF-A, Schlaffragebogen SF-A und SF-B.

[g] IQR, Saint Mary's Hospital Questionnaire.

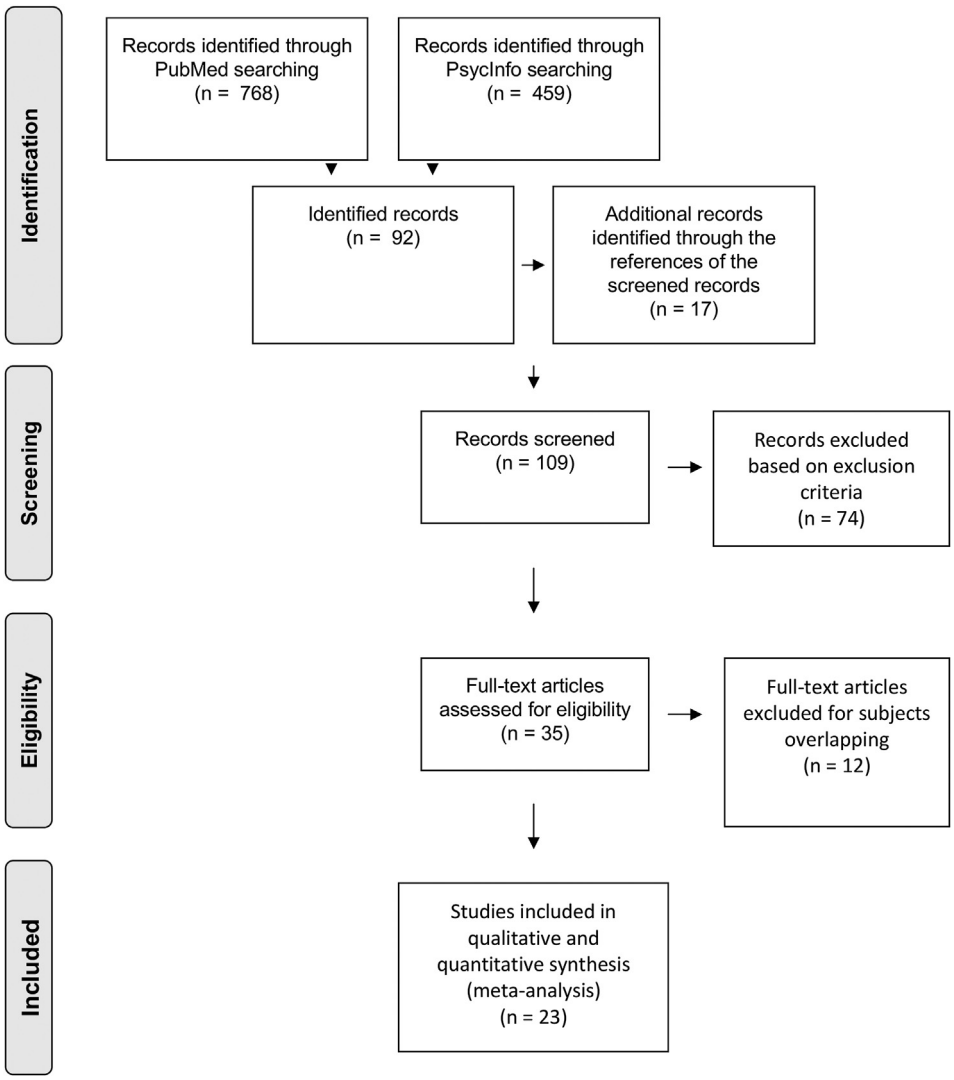

Fig. 1. The search flow: results of search for articles.

demographic and other methodological variables; and "blindness"of the sleep scoring. The sample size ranged from 12 participants (6 people with PI and 6 GSCs)[61] to 200 participants (100 people with PI and 100 GSCs).[50] Thirteen studies reported information about socio-demographic characteristics of the PI and GSC group. Education levels were evaluated in seven studies,[45,46,49,50,52,59,62] Body mass index in four studies,[48,55,56,66] marital status in three studies,[45,46,62] ethnicity in two studies,[49,62] employment status in two studies,[45,62] and income,[62] retirement status,[46] social status,[50] smoking,[61] depression and anxiety scores[52] in one study, respectively.

In seven studies, it was specified that the scorers of the PSG recordings were blind to participants' diagnosis,[46,49,52,60–62,66] while all other studies did not specify this.

Meta-analytic calculations: PSG variables

In the present meta-analysis, we analyzed the following number of studies for each PSG variables: SEI (22 studies); SOL (20 studies); TST (20 studies); TIB (6 studies); NA (9 studies); REML (11 studies); S1 min (6 studies); S1 % (15 studies); S2 min (6 studies); S2 % (16 studies); SWS min (6 studies); SWS % (16 studies); REM min (5 studies); REM % (16 studies); WASO min (12 studies); WASO % (6 studies). Table 2 shows for each study which PSG variables were considered.

Meta-analytic calculations: sensitivity analyses for outlier detection

The study conducted by Vgontzas et al.[66] was found to be a possible outlier for SEI, SOL, S2 %, SWS %, and WASO min. The study by Merica et al.[58] was found to be a possible outlier for SEI, TST, and S1 min. The studies by Edinger et al.[49] and Lushington et al.[57] were identified as possible outliers for SEI and WASO min. Additionally, the study by Lushington et al.[57] was found to be a possible outlier also for TST. Finally, the study conducted by Hajak et al.[53] was found to be a possible outlier for REM %. For this reason, these studies were not considered further in the meta-analyses for the respective sleep parameters. No indication for possible outliers was found for TIB, NA, REML, S1 %, S2 min, SWS min, REM min, and WASO %.

Meta-analytic calculations: general results

Table 3 shows the results for the PSG variables for all studies after exclusion of possible outliers. A graphical summary of the results for all studies is provided in Fig. 2.

Table 2
Sleep variables.

PSG sleep variables	SEI	SOL	TST	TIB	NA	REML	S1 (min or %)	S2 (min or %)	SWS (min or %)	REM (min or %)	WASO (min or %)
Bastien et al., 2008[45]	X	X	X		X	X	X %	X %	X %	X %	X min
Bastien et al., 2008[45]	X	X	X		X	X	X %	X %	X %	X %	X min
Bastien et al., 2003[46]	X	X	X	X			X %	X %	X %	X %	X min
Buysse et al., 2008[47]	X	X	X	X			X %	X %	X %		X min
De Zambotti et al., 2011[48]	X	X	X		X	X	X min	X min	X min	X min	X min
Edinger et al., 2001[49]	X	X	X			X	X min	X min	X min	X min	X min
Feige et al., 2008[50]	X	X	X		X	X	X %	X %	X %	X %	X %
Ferri et al., 2009[51]	X	X	X	X	X	X	X %	X %	X %	X %	X %
Forget et al., 2011[52]	X	X	X				X %	X %	X %	X %	X min
Hajak et al., 1995[53]	X	X	X	X	X	X	X %	X %	X %	X %	
Irwin et al., 2003[54]	X	X	X			X	X %	X %	X %	X %	
Jurysta et al., 2009[55]	X	X	X	X	X		X min	X min	X min	X %	X %
Lanfranchi et al., 2009[56]	X	X	X				X %	X %	X %	X %	X min
Lushington et al., 1999[57]	X	X	X	X	X	X	X %	X %	X %	X %	X min
Merica et al., 1998[58]	X		X				X min	X min	X min	X min	
Niemcewzicz et al., 2001[59]	X	X	X			X	X %	X %	X %	X %	X %
Parrino et al., 2009[60]		X	X		X		X %	X %	X %	X %	
Salin-Pascual et al., 2006[61]	X						X %	X %	X %	X %	X %
Savard et al., 2003[62]	X										
Sforza and Haba-Rubio 2006[63]	X	X	X		X		X min	X min	X min	X min	X min
Siversten et al., 2009[64]	X	X	X				X min	X min	X min	X min	X min
Staner et al., 2003[65]	X	X	X			X	X %	X %	X %	X %	X %
Toussaint et al., 1995[38]	X	X	X			X		X %	X %	X %	X min
Vgontzas et al., 2002[66]	X	X					X %	X %	X %	X %	X min

Abbreviations: %, duration expressed as percentage; min, duration expressed in minutes; NA, number of awakenings; REM, duration of REM sleep; REML, REM latency; S1, duration of stage 1; S2, duration of stage 2; SEI, sleep efficiency index; SOL, sleep onset latency; SWS, duration of slow wave sleep; TIB, total time in bed; TST, total sleep time; WASO, wake after sleep onset.

Subjects with PI, compared to GSC, present significant impairments of both sleep continuity and sleep architecture. With respect to sleep continuity, PI patients show a reduced SEI (Fig. S1), longer SOL, shorter TST, and increased NA. With respect to sleep architecture, PI patients spend less time in SWS (Fig. S2) and more time awake after sleep onset (WASO, Fig. S3). Moreover, PI patients spend less time in REM sleep compared to GSC (Fig. S4). Finally, no significant difference between groups was found for REM latency (Fig. S5).

The I^2 index shows that the studies share moderate to high heterogeneity for almost all the meta-analyses conducted, excluding REML, S1 min, and WASO min for which the studies show low heterogeneity ($I^2 < 50\%$). Based on the observation that the studies differ in many aspects (e.g., study population, definition of the sleep variables, diagnostic instruments, duration of PI, and subtype of PI) further subgroup analyses were conducted for all sleep parameters.

Meta-analytic calculations: subgroup analyses

The following moderator variables were taken into account in subgroup analyses: 1) age; 2) sex; 3) definition of the sleep variables; 4) definition of PI based on objective criteria; and 5) duration of PI. Subgroup analyses were conducted only when at least four studies were available.

Age

With respect to age, meta-analytic calculations were repeated by including only the studies evaluating participants in the age group between 18 and 60 y. It was not possible to conduct the analysis for TIB and S1 min as there were less than four studies. With respect to the results, SWS % and min were no longer significantly different between groups, although a trend for SWS % was observed ($p = 0.06$) suggesting a reduced duration of this stage in patients with PI. All other results were similar to the ones observed in the analyses of all studies reported above. High heterogeneity was found for S2 min, SWS min, and REM min ($I^2 > 80\%$). Small to moderate heterogeneity was found for all other variables, excluding REML. For this variable, I^2 was close to zero indicating that the heterogeneity between the studies may be explained by random error. However, this result may also be influenced by the low power of the analysis due to the reduction of the sample size. The results of these subgroup analyses are summarized in Table S2.

Sex

With respect to sex, meta-analytic calculations were repeated after exclusion of the two studies evaluating only male participants.[54,55] No analyses were conducted for REM min, WASO % and WASO min because for these variables all the included studies evaluated mixed samples of women and men. With respect to the main results, we found only a trend for a reduced REM sleep duration in patients with PI compared to GSC ($p = 0.06$). However, the lack of significance may result from the reduction of the sample size due to the subgroup analysis. High heterogeneity was found for TIB, S1 %, S2 min, and SWS min ($I^2 > 80\%$). Moderate heterogeneity was found for SEI, SOL, TST, NA, S2 %, SWS %, and REM % ($I^2 > 50$ and $<80\%$). Low heterogeneity was found for REML and S1 min ($I^2 < 50\%$). The results are summarized in Table S3.

Definition of the sleep variables

Different definitions between the studies were found for the following sleep variables: SEI; SOL; NA; and REML. No subgroup analysis with respect to the definition was conducted for TST and TIB, as these were always defined as the total time spent asleep during the night or as the total time spent in bed. With respect to the duration of the sleep stages S1, S2, SWS, and REM sleep as well as with respect to WASO, no subgroup analysis was conducted as we could not divide the studies into subgroups.

Table 3
Meta-analytic calculations: general results.

Sleep variable	Patients with PI	Good sleeper controls	Meta-analytic calculations	Results[a]	I^2 index
SEI	$N = 482$ Mean ± sd = 81.8 ± 10.5	$N = 384$ Mean ± sd = 88.8 ± 6.7	$d = -0.7$; SE = 0.1; z-value = −5.9, $p < 0.001$	−	60.5
SOL	$N = 528$ Mean ± sd = 20.0 ± 17.1	$N = 430$ Mean ± sd = 14.2 ± 11.3	$d = 0.3$; SE = 0.1; z-value = 2.4, $p = 0.02$	+	75.2
TST	$N = 512$ Mean ± sd = 391.1 ± 53.4	$N = 414$ Mean ± sd = 414.8 ± 46.3	$d = -0.6$; SE = 0.1; z-value = −4.1, $p < 0.001$	−	71.3
TIB	$N = 123$ Mean ± sd = 483.6 ± 33.9	$N = 88$ Mean ± sd = 478.5 ± 46.0	$d = -0.3$; SE = 0.5; z-value = 0.7, $p = 0.46$	·	88.7
NA	$N = 233$ Mean ± sd = 17.9 ± 8.8	$N = 203$ Mean ± sd = 12.0 ± 5.8	$d = 0.8$; SE = 0.2; z-value = 4.1, $p < 0.001$	+	63.4
REML	$N = 327$ Mean ± sd = 89.3 ± 38.7	$N = 291$ Mean ± sd = 87.1 ± 36.4	$d = 0.04$; SE = 0.1; z-value = 0.4, $p = 0.7$	·	25.6
S1 %	$N = 355$ Mean ± sd = 7.0 ± 3.4	$N = 319$ Mean ± sd = 6.8 ± 2.8	$d = 0.1$; SE=0.2; z-value=0.5, $p = 0.6$	·	80.6
S1 min	$N = 134$ Mean ± sd = 37.4 ± 21.5	$N = 96$ Mean ± sd = 40.6 ± 16.4	$d = -0.1$; SE = 0.2; z-value = −0.3, $p = 0.8$	·	40.0
S2 %	$N = 400$ Mean ± sd = 53.8 ± 8.1	$N = 348$ Mean ± sd = 54.4 ± 6.8	$d = -0.05$; SE = 0.1; z-value = −0.4, $p = 0.7$	·	63.5
S2 min	$N = 154$ Mean ± sd = 209.7 ± 34.8	$N = \ = 115$ Mean ± sd = 215.1 ± 38.7	$d = -0.5$; SE = 0.4; z-value = −1.2, $p = 0.2$	·	89.7
SWS %	$N = 400$ Mean ± sd = 10.9 ± 7.4	$N = 340$ Mean ± sd = 12.8 ± 6.7	$d = -0.4$; SE = 0.2; z-value = −2.8, $p = 0.005$	−	68.4
SWS min	$N = 154$ Mean ± sd = 70.7 ± 25.7	$N = 115$ Mean ± sd = 90.7 ± 25.7	$d = -1.1$; SE = 0.4; z-value = −2.6, $p = 0.01$	−	88.3
REM %	$N = 367$ Mean ± sd = 20.3 ± 5.1	$N = 335$ Mean ± sd = 22.3 ± 4.8	$d = -0.4$; SE = 0.2; z-value = −2.7, $p = 0.008$	−	72.3
REM min	$N = 140$ Mean ± sd = 78.9 ± 21.7	$N = 101$ Mean ± sd = 89.6 ± 13.0	$d = -1.4$; SE = 0.7; z-value = −2.1, $p = 0.03$	−	93.9
WASO %	$N = 177$ Mean ± sd = 17.0 ± 11.1	$N = 169$ Mean ± sd = 11.0 ± 6.9	$d = 0.6$; SE = 0.3; z-value = 2.1, $p = 0.04$	+	78.9
WASO min	$N = 261$ Mean ± sd = 58.5 ± 43.1	$N = 160$ Mean ± sd = 36.8 ± 25.5	$d = 1.3$; SE = 0.4; z-value = 3.4, $p = 0.001$	+	35.1

Abbreviations: NA, number of awakenings; REM, duration of REM sleep; REML, REM latency; S1, duration of stage 1; S2, duration of stage 2; SEI, sleep efficiency index; SOL, sleep onset latency; SWS, duration of slow wave sleep; TIB, total time in bed; TST, total sleep time; WASO, wake after sleep onset.
[a] Following the code used in Benca et al. 1992[37]: minus sign indicates significantly less than control value at $p < 0.05$; plus sign indicates significantly more than control value at $p < 0.05$; dot indicates no significant group differences. *d*, standardized mean effect size; SE, standard error.

With respect to SEI, the analyses were repeated including only six studies in which the definition was specified as the ratio between TST and TIB.[50–53,56,62] Eleven studies were excluded as they did not specify the definition.[38,46–48,54–55,59,61,63–65] One study was excluded as it reported a different definition[45] (SEI = TST/total recording time).

With respect to SOL, the analyses were repeated considering only four studies in which the definition was specified as latency to stage 2 sleep.[45,50,53,65] Eleven studies were excluded as they did not specify the definition,[46–48,51–52,54–55,57,59,63–64] and three studies were excluded as they reported different definitions (in two studies, sleep onset latency was defined as the latency to any sleep stage[49,56]; in one study, sleep onset latency was defined as the latency to any sleep stage excluding stage 1[38]).

With respect to NA, the analyses were repeated for four studies which considered the total NA.[48,50,53,55] Three studies were excluded as they used different definitions,[51,57,63] and one study was excluded as it did not report the definition of the variable.[45]

With respect to REML, the analyses were repeated including only three studies with a consistent definition of time between sleep onset, defined as the latency to stage 2 and REM sleep.[45,50,53] Two studies were excluded as they reported a different definition (see definitions for sleep onset[38,49]). Six studies were excluded because no definition was reported.

With respect to the results, SOL defined as the latency to stage 2 sleep did not differ between people with PI and GSC anymore. A high heterogeneity between the studies was found for SOL ($I^2 = 83.2$), showing that the variability may be better explained by other factors. For the other variables (SEI, NA, and REML), the observed $I^2 = 0.00$ indicates that the variability between the studies may completely depend on random error. However, these results may be also explained by the small sample size in these subgroup analyses (six, four and four studies, respectively). The results are summarized in Table S4.

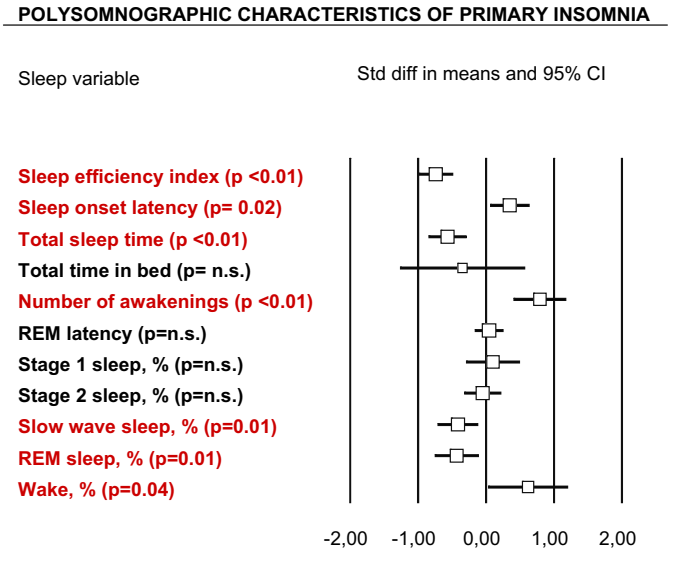

Fig. 2. Graphical summary of the general results: Polysomnographic characteristic of patients with primary insomnia as compared to good sleepers controls. Std diff, standardized difference; CI, confidence interval.

Insomnia based on the subjective complaint only

Five studies diagnosed PI patients also on the basis of their PSG profile[45,53,55,58,60,66] (see Table 1 for details). The meta-analytic analyses were repeated after the exclusion of these five studies.

The results are presented in Table 4. REM % and REM min did not differ between patients with PI and GSC anymore (respectively $p = 0.08$ and $p = 0.2$). Moreover, WASO % was no longer significantly different between the groups ($p = 0.14$). However, when it was calculated in minutes, PI still presented an increased WASO min as compared to GSC ($p < 0.001$). One explanation for this difference might be that two of the excluded studies focused mainly on patients with specific problems in sleep maintenance. Studies shared high heterogeneity for TIB, and REM min ($I^2 > 80\%$). Moderate heterogeneity was found for SEI, SOL, TST, NA, S1 %, S2 %, S2 min, SWS %, SWS min, REM %, and WASO % ($I^2 > 50$ and $<80\%$). Studies shared low heterogeneity for REML, S1 min, and WASO min ($I^2 < 50$).

Duration of insomnia

The last subgroup analysis focused on studies including patients with an average PI duration >5 y.[45,46,49,52,53,56,59] The aim of this subgroup analysis was to identify any possible change in the sleep profile of patients with PI due to chronicity.

The results are summarized in Table 5. Patients with chronic PI present a reduced SEI and an increased time spent awake during the night after sleep onset (WASO min). However, there were no significant differences to GSC in SOL, TST, REML, S1 %, S2 %, SWS %, and REM %. Moderate heterogeneity was found for SOL and TST ($I^2 > 50$ and $<80\%$). Low heterogeneity was found for S2 % and REM % ($I^2 < 50$). With respect to SEI, REML, S1 %, and WASO min, we found I^2 close to 0, which, as mentioned above, could indicate a low power of the analyses.

Sleep diaries

In our study sample, 13 studies collected subjective ratings of sleep quantity and quality. In four studies, participants were required to fill in a post-sleep self-report after the nights spent in the sleep laboratory.[47,50,60,63] Of these four studies, two also used a sleep diary for 1 week,[47,63] but only in one study the data of the sleep diary were reported.[47] In the other study, the diaries were exclusively used in the screening procedure and data were not presented in the text.[63] Other four studies used sleep diaries exclusively for screening purposes without reporting data in the text.[46,48,54,57] In total, six studies analyzed data from sleep diaries filled in for 1, 2 or 3 weeks, and these were further evaluated with meta-analytic calculations[45,47,52,56,62,64] (for more details see Table 1). Fig. 3 shows the four Forest plots related to each of the four sleep variables we could analyze with meta-analytic computations: SEI, SOL, TST, WASO. TIB was not evaluated in the meta-analytic calculations as only three studies reported it.

Sleep diaries data show severe impairments in all evaluated sleep variables. Specifically, with respect to SEI, a total of 184 patients with PI with a mean SEI of 69.8 ± 11.9% were compared with 110 GSC with a mean SEI of 93.2 ± 4.0%. Considering SOL,

Table 4
Meta-analytic calculations: Results related to studies which defined insomnia based exclusively on the subjective complaint.

Sleep variable	Patients with insomnia	Good sleeper controls	Meta-analytic calculations	Results[a]	I^2 index
SEI	$N = 443$ Mean ± sd = 82.4 ± 10.6	$N = 358$ Mean ± sd = 89.0 ± 6.8	$d = -0.7$; SE = 0.1; z-value = −5.7, $p < 0.001$	−	54.4
SOL	$N = 469$ Mean ± sd = 20.7 ± 18.7	$N = 384$ Mean ± sd = 14.2 ± 11.7	$d = 0.4$; SE = 0.2; z-value = 2.2, $p = 0.03$	+	78.7
TST	$N = 453$ Mean ± sd = 390.9 ± 55.8	$N = 368$ Mean ± sd = 413.5 ± 45.4	$d = -0.6$; SE = 0.2; z-value = −3.5, $p < 0.001$	−	76.8
TIB	$N = 99$ Mean ± sd = 482.0 ± 25.2	$N = 69$ Mean ± sd = 484.7 ± 46.2	$d = -0.7$; SE = 0.6; z-value = −1.1, $p = 0.3$	·	92.1
NA	$N = 174$ Mean ± sd = 11.3 ± 6.2	$N = 157$ Mean ± sd = 8.8 ± 4.9	$d = 0.6$; SE = 0.3; z-value = 2.3, $p = 0.02$	+	71.7
REM L	$N = 302$ Mean ± sd = 84.1 ± 32.7	$N = 279$ Mean ± sd = 82.6 ± 34.3	$d = 0.04$; SE = 0.1; z-value = 0.3, $p = 0.8$	·	37.4
S1 %	$N = 299$ Mean ± sd = 7.4 ± 3.7	$N = 276$ Mean ± sd = 7.4 ± 3.1	$d = 0.1$; SE = 0.2; z-value = 0.5, $p = 0.6$	·	79.5
S1min	$N = 120$ Mean ± sd = 38.3 ± 21.3	$N = 82$ Mean ± sd = 43.8 ± 16.7	$d = -0.1$; SE = 0.2; z-value = −0.7, $p = 0.5$	·	48.0
S2 %	$N = 355$ Mean ± sd = 54.3 ± 8.7	$N = 316$ Mean ± sd = 55.2 ± 6.8	$d = -0.07$; SE = 0.1; z-value = −0.6, $p = 0.6$	·	57.3
S2min	$N = 120$ Mean ± sd = 199.6 ± 36.8	$N = 82$ Mean ± sd = 198.5 ± 42.4	$d = -0.02$; SE = 0.3; z-value = −0.07, $p = 0.9$	·	74.5
SWS %	$N = 355$ Mean ± sd = 10.3 ± 7.0	$N = 308$ Mean ± sd = 11.9 ± 6.7	$d = -0.4$; SE = 0.2; z-value = −2.4, $p = 0.02$	−	69.0
SWSmin	$N = 120$ Mean ± sd = 77.7 ± 27.0	$N = 82$ Mean ± sd = 97.2 ± 22.8	$d = -0.8$; SE = 0.3; z-value = −2.3, $p = 0.02$	−	77.2
REM %	$N = 307$ Mean ± sd = 20.1 ± 5.7	$N = 283$ Mean ± sd = 21.9 ± 4.8	$d = -0.3$; SE = 0.2; z-value = −1.7, $p = 0.08$	·	64.4
REMmin	$N = 120$ Mean ± sd = 76.1 ± 25.5	$N = 82$ Mean ± sd = 82.1 ± 15.2	$d = -0.6$; SE = 0.5; z-value = −1.3, $p = 0.2$	·	88.5
WASO %	$N = 163$ Mean ± sd = 16.5 ± 11.6	$N = 155$ Mean ± sd = 11.9 ± 7.7	$d = 0.4$; SE = 0.3; z-value = 1.5, $p = 0.14$	·	70.9
WASO min	$N = 246$ Mean ± sd = 61.1 ± 45.3	$N = 153$ Mean ± sd = 38.0 ± 25.4	$d = 0.6$; SE = 0.1; z-value = 3.8, $p < 0.001$	+	41.6

Abbreviations: NA, number of awakenings; REM, duration of REM sleep; REML, REM latency; S1, duration of stage 1; S2, duration of stage 2; SEI, sleep efficiency index; SOL, sleep onset latency; SWS, duration of slow wave sleep; TIB, total time in bed; TST, total sleep time; WASO, wake after sleep onset.

[a] Following the code used in Benca et al.[37]: minus sign indicates significantly less than control value at $p < 0.05$; Plus sign indicates significantly more than control value at $p < 0.05$; Dot indicates no significant group differences. *d*, standardized mean effect size; SE, standard error.

Table 5
Meta-analytic calculations: Results related to studies with PI duration on average >5 y.

Sleep variable	Patients with insomnia	Good sleeper controls	Meta-analytic calculations	Results[a]	I^2 index
SEI	$N = 96$ Mean ± sd = 83.9 ± 9.2	$N = 77$ Mean ± sd = 88.3 ± 7.7	$d = -0.4$; SE = 0.2; z-value = −2.7, $p = 0.008$	–	0.00
SOL	$N = 129$ Mean ± sd = 16.5 ± 10.9	$N = 112$ Mean ± sd = 15.8 ± 11.7	$d = 0.09$; SE = 0.2; z-value = −0.4, $p = 0.7$	·	65.9
TST	$N = 129$ Mean ± sd = 387.6 ± 40.4	$N = 112$ Mean ± sd = 403.9 ± 47.2	$d = -0.5$; SE = 0.3; z-value = −1.7, $p = 0.1$	·	77.8
TIB[b]					
NA[b]					
REM L	$N = 89$ Mean ± sd = 97.7 ± 42.8	$N = 71$ Mean ± sd = 98.3 ± 41.6	$d = 0.1$; SE = 0.2; z-value = −0.7, $p = 0.5$	·	0.00
S1 %	$N = 96$ Mean ± sd = 6.8 ± 3.7	$N = 77$ Mean ± sd = 6.0 ± 3.0	$d = 0.3$; SE = 0.2; z-value=1.7, $p = 0.09$	·	0.00
S1min[b]					
S2 %	$N = 96$ Mean ± sd = 56.0 ± 7.7	$N = 77$ Mean ± sd = 56.1 ± 7.4	$d = 0.005$; SE = 0.2; z-value=0.03, $p = 1.0$	·	33.4
S2min[b]					
SWS %	$N = 96$ Mean ± sd = 10.2 ± 7.8	$N = 77$ Mean ± sd = 11.5 ± 7.2	$d = -0.3$; SE = 0.2; z-value=−1.7, $p = 0.09$	·	0.00
SWSmin[b]					
REM %	$N = 86$ Mean ± sd = 22.4 ± 5.3	$N = 72$ Mean ± sd = 23.4 ± 5.2	$d = -0.2$; SE = 0.2; z-value=−1.2, $p = 0.2$	·	23.6
REMmin[b]					
WASO %[b]					
WASO min	$N = 70$ Mean ± sd = 53.5 ± 36.8	$N = 56$ Mean ± sd = 36.7 ± 30.2	$d = 0.4$; SE = 0.2; z-value=1.9, $p = 0.05$	+	0.00

Abbreviations: NA, number of awakenings; REM, duration of REM sleep; REML, REM latency; S1, duration of stage 1; S2, duration of stage 2; SEI, sleep efficiency index; SOL, sleep onset latency; SWS, duration of slow wave sleep; TIB, total time in bed; TST, total sleep time; WASO, wake after sleep onset.

[a] Following the code used in Benca et al., 1992[37]: minus sign indicates significantly less than control value at $p < 0.05$; plus sign indicates significantly more than control value at $p < 0.05$; dot indicates no significant group differences.

[b] Less of four studies after exclusion of possible outliers. *d*, standardized mean effect size; SE, standard error.

137 patients with PI reported a mean time of 39.7 ± 33.7 min to fall asleep compared with 76 GSC reporting a mean SOL of 10.2 ± 8.7 min. With respect to TST, 167 patients with PI reported 341.0 ± 66.3 min per night compared with 91 GSC reporting 458.1 ± 47.1 min per night. Finally, 167 patients with PI estimating to be awake 111.9 ± 47.8 min per night (WASO) were compared with 91 GSC estimating to be awake 18.3 ± 16.2 min per night.

Moderate heterogeneity was found for each analysis ($I^2 >$ 50 and <80%), excluding the one related to SOL that showed I^2 close to 0.

Power spectral analyses (PSA)

We could not perform a meta-analytic calculation for PSA as the published studies were methodologically too different to be compared. In total, seven studies conducted PSA. In one study, PSA was exclusively used for correlations with other physiological variables, specifically cardiac vagal influence.[55] In the other six studies, the quantity and the time course of the different frequency rhythms were evaluated showing, however, different methodological approaches and different findings. The results are summarized in Table 6.

Discussion

Polysomnographic profile of people with PI

The current meta-analysis indicates that PI seems to be characterized by impairments in both sleep continuity and sleep architecture. More specifically, compared with GSC, patients with PI sleep about 23 min less; take on average 6 min longer to fall asleep; and present about six awakenings more per night. These alterations in sleep continuity result in a reduced SEI that, in patients with PI, was below the generally considered threshold for "good sleep" of 85%. Surprisingly patients with PI, compared to GSC, seem to spend significantly less time in SWS and REM sleep. Up to now, alterations of sleep architecture have not been listed among the typical polysomnographic changes in patients with PI. The significant difference between patients with PI and GSC for both SWS and REM sleep manifests itself by 2% less for both sleep stages. In minutes, patients with PI spend 20 min less in SWS and 10 min less in REM sleep in comparison to GSC. The loss of both sleep stages seems more relevant, when considering it from a long-term perspective: for a month it would correspond to a loss of 600 min of SWS and 300 min of REM sleep. In addition, PI patients spend about 20 min more awake during the night after sleep onset compared to GSC, which calculated over a month corresponds to 600 min.

In Table 7 we have compared our data (i.e., means ± standard deviations), with recently published PSG data in sleep disorders and other psychological disorders, namely, restless legs syndrome (RLS),[67] obstructive sleep apnea (OSA),[68] major depressive disorder (MDD,[69,70] see also the meta-analysis by Pillai et al.[71]), and post-traumatic stress disorder (PTSD,[72] see also the meta-analysis by Kobayashi et al.[73]). With respect to MDD and PTSD we did not use the meta-analytic studies for comparison as they did not report means and standard deviations of each single study included. The comparison of the results for the different disorders can be performed only at a descriptive level as the datasets differ for age and gender. However, from this comparison, some ideas for future research can be deduced. SEI is comparable for patients with PI, MDD, and OSA. RLS appears to be coupled with a more severe impairment of sleep continuity in comparison to the other disorders. In contrast, patients with PTSD seem to display only minor PSG documented sleep disruptions. While RLS and OSA are

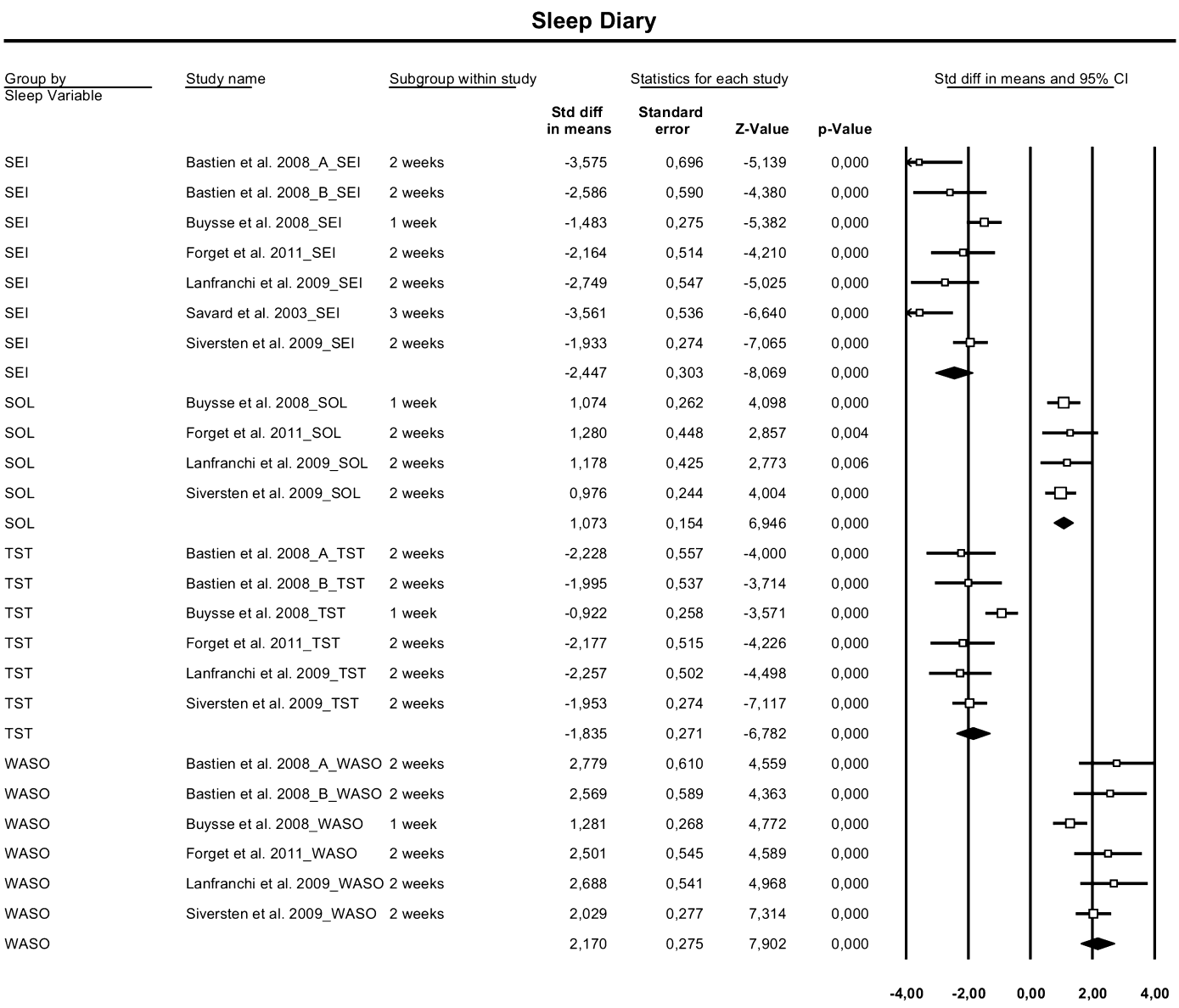

Fig. 3. Summarizing effect sizes for the sleep variables derived from sleep diaries and considered for the meta-analytic calculations (all the meta-analytic calculations were done using a random-effect meta-analytic model). SEI, sleep efficiency index; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset.

associated with the shortest TST, our results indicate that patients with PI have a TST similar or slightly smaller than patients with MDD. SOL seems to be mildly prolonged in PI, RLS and OSA, and more severely in MDD. Although only a moderate reduction of SWS characterizes PI, this seems to be comparable with the alteration found in PTSD. Finally, patients with PI have increased WASO, similar to those with MDD. PTSD seems to be associated with a less severe problem of wake time during the night, while RLS patients may experience a more severe problem with respect to the wake duration. To summarize, the polysomnographically detected values of SEI, TST, SOL, and WASO in PI seem to be similar to those in other psychiatric or sleep disorders for which is generally accepted that there are polysomnographic sleep alterations.

In addition, with respect to REM sleep, patients with PI do not present a reduced REM latency and a prolonged REM sleep duration as found for patients with MDD. In contrast, we found that REM sleep in patients with PI, as compared with GSC, is reduced. Thus, the condition of PI seems to be associated with a specific sleep profile, which is in line with the state-of-the-art view of insomnia as a diagnostic entity independent from affective disorders (for a review, see[74]).

Subgroup analyses

Whenever possible we conducted subgroup analyses in order to explore the sources of variability between the studies and to better understand the sleep changes in relation to different intervening variables. Yet, for this type of analysis we often had to evaluate the role of possible intervening factors by excluding them, rather than by evaluating them. For example, we could not analyze a group of studies conducted on an elderly population; we could only analyze our sample of studies after excluding those studies which included also elderly participants. The same problem was encountered for the factor sex and duration of PI. In addition, only few calculations

Table 6
Power spectral analysis.

Study	Sleep stages	EEG derivations	PSA calculation	Artefacts detection	Bands	Analyses	Results
Bastien et al., 2003[46]	NREM sleep (stage 2, 3 and 4) of the first 4 cycles	C3-A2	Consecutive 2.56-s epochs with no overlap	Artefacts, including extreme REMs and muscular or cardiac activity, were visually removed. Other EEG segments that may have contained artefacts were removed through specific software. EEG frequency of the higher 35–100 Hz was removed.	Delta (0–3.9) Theta (3.9–7.02) Alpha (7.02–11.7) Sigma (11.7–14.04) Beta1 (14.04–21.84) Beta2 (21.84–30.03)	One-way ANOVAs were performed on the average absolute power for each frequency band during the 4 cycles and for the total night mean on the combined NREM sleep stage 2, 3 and 4. Moreover, one-way ANOVAs were performed in order to explore in which sleep stage (2 vs 3 and 4) absolute frequency band power differed.	No group difference
Buysse et al., 2008[47]	Whole night NREM sleep	C4 − A1 + A2 or C3 − A1 + A2	Non-overlapping 4-s epochs	Low frequency artefacts were excluded by eliminating epochs scored as wakefulness or movement time. High frequency artefacts by applying to 4 s epochs a threshold for high EEG frequencies (26.25–32 Hz).	Delta (0.5–4) Theta (4–8) Alpha (8–12) Beta (16–32) Sigma (12–16) Gamma (32–50)	Six repeated measures mixed effect models for each band. Factors included Group, NREM period number (1–4) and interactions Group*sex and Group*cycle. Absolute power was considered.	Highest power for delta, theta, sigma, beta and gamma in women with insomnia. Women with insomnia had higher power than good sleepers women for frequencies in the high delta-low theta range across all NREM periods.
Forget et al., 2011[52]	NREM sleep (stage 2)	Not specified	1 s spectral windows non-overlapping	Not specified	Delta (1–4) Theta (4–8) Alpha (8–12) Beta (14–35) Sigma (12–14) Gamma (35–60) Omega (60–125)	Anovas with respect to trials containing spontaneous *K*-complexes	Changes surrounding the spontaneous *K*-complex: Less activity in the alpha frequency band found only in controls.
Lanfranchi et al., 2009[56]	Whole night NREM sleep	C3–C4 and F3–F4	4-s artefact-free sections	Artefacts were detected automatically as well as by visual inspection.	Beta (16–32)	Spectral power was obtained by fast Fourier transforms performed on 4-s artefact-free sections using a cosine window tapering, resulting in a 0.25 Hz spectral resolution.	Patients with PI had greater EEG activity in beta frequencies with respect to controls
Merica et al., 1998[58]	NREM and REM episodes during the first 4 NREM-REM cycles	F4-Cz	Consecutive 4-s epochs	These epochs which presented an artefact on the visual trace were coded as missing data so as to preserve time continuity.	Delta (0.5–3.75) Theta (3.75–6.75) Alpha (6.75–12.5) Beta (14.75–30) Sigma (12.5–14.75)	The time course (average power curves) of the absolute power in each band was analyzed separately in each of the NREM and REM episodes during the first four NREM-REM cycles.	In the NREM the rise rates for all the frequencies below the beta range are slower and the level reached lower in the group with insomnia, whereas beta power is significantly increased. In REM, increased power in the faster frequency bands, together with a deficit in the delta and theta bands, differentiate the people with insomnia. The height of the first sigma peak tends to be lower and wider in the group with insomnia.

Staner et al., 2003[65]	Each epoch scored either as wake or stage 1 sleep during the sleep onset period (defined as latency to stage 2 sleep). Each epoch scored as stage 2, 3 or 4 during the first NREM period (defined as latency from sleep onset and first REM period)	C3−A2	2-s Interval	Epochs containing movement, breathing or muscle artefacts or recording difficulties were excluded.	Delta (0.5−3.5) Theta (4−7.5) Alpha (8−12.5) Beta1 (13−21.5) Beta2 (22−30)	Dynamics of standardized EEG power density within the sleep onset period and the first NREM periods were analyzed by means of Group × Interval Anovas.	Group effects were evidenced for beta 1 during the sleep onset period and for delta power during the last 5 min before sleep onset, both being found lower in the group with insomnia. People with insomnia did not experience a gradual decrease of their alpha and beta 1 power across intervals during the sleep onset period.

Abbreviations: EEG, electroencephalography; NREM, non-REM sleep; PI, primary insomnia; PSA, power spectral analysis; REM, rapid eye movement sleep.

Table 7
Comparisons with other sleep and psychiatric disorders.

Data	RLS	OSA		MDD		PTSD	PI	GSC
Data source	Hornjak et al., 2007[67]	Bianchi et al., 2010[68]: Mild OSA	Bianchi et al., 2010[68]: Severe OSA	Lopes et al., 2007[69]	Leistedt et al., 2007[70]	Breslau et al., 2004[72]	The present study	The present study
N (sample size)	45	496	338	15	10	71	582	485
Age (mean ± sd)	47.4 ± 10.9	63.8 ± 10.3	63.7 ± 10.5	38	41.7 ± 8.1	37.6 ± 1.7 (given on the entire sleep study sample, including also no-PTSD participants)	42.9 ± 8.9	40.0 ± 8.1
Gender (% F)	64.4	30	29.3	47	Not given	66.1	51.7	53.3
SEI	72.4 ± 16.5	81.7 ± 10.2	79.4 ± 11.2	85.1 ± 9.9	81.1	85.5 ± 10.2	81.8 ± 10.5	88.8 ± 6.7
TST	345.2 ± 80.2	326.5 ± 61.9	344.2 ± 61.7	405.4 ± 238.5	401.3 ± 87.8		391.1 ± 53.4	414.8 ± 46.3
SOL	19.9 ± 24.5	23.1 ± 22.5	22.9 ± 21.4		34.8 ± 30.1	21.6 ± 23.2	20.0 ± 17.1	14.2 ± 11.3
REML	123.1 ± 73.0	86.0 ± 56.4	102.6 ± 69.3	111.7 ± 65.8	57.8 ± 21.9	92.4 ± 42.2	89.3 ± 38.7	87.1± 36.4
S1	11.6 ± 4.9%	5.8 ± 4.3%	6.4 ± 4.3%	15.7 ± 8.4 min	10.7 ± 6.7%	12.3 ± 5.8%	7.0 ± 3.4% 37.4 ± 21.5 min	6.8 ± 2.8% 40.6 ± 16.4 min
S2	46.0 ± 6.0%	59.3 ± 10.7%	63.1 ± 11.9%	266.0 ± 84.4 min	57.1 ± 6.7%	55.7 ± 6.6%	53.8 ± 8.1% 209.7 ± 34.8 min	54.4 ± 6.8% 215.1 ± 38.7 min
SWS	4.2 ± 6.0%			57.7 ± 71.3 min	7.5 ± 3.8%	11.4 ± 8.0%	10.9 ± 7.4% 70.7 ± 25.7 min	12.8 ± 6.7% 90.7 ± 25.7 min
REM	15.0 ± 6.1%	19.4 ± 6.0 min	17.3 ± 6.4 min	63.8 ± 44.9 min	23.1 ± 6.7%	20.3 ± 5.2%	20.3 ± 5.1% 78.9 ± 21.7 min	22.3 ± 4.8% 89.6 ± 13.0 min
WASO	23.0 ± 16.1%			68.0 ± 44.9 min	14.4 ± 9.4%	50.3 ± 36.2 min	17.0 ± 11.1% 58.5 ± 43.1 min	11.0 ± 6.9% 36.8 ± 25.5 min

Blank spaces indicate lack of information. When standard deviations are not reported, these were not given in the text.
Abbreviations: GSC, good sleeper controls; MDD, major depressive disorder; OSA, obstructive sleep apnea; PI, patients with primary insomnia; PTSD, post-traumatic stress disorder; REM, duration of REM sleep; REML, REM latency; S1, duration of stage 1; S2, duration of stage 2; SEI, sleep efficiency index; SOL, sleep onset latency; SWS, duration of slow wave sleep; TST, total sleep time; WASO, duration of wake after sleep. onset.

could be performed with respect to different definitions of the sleep variables as often this information was not specified in the studies. Moreover, anytime we considered different subgroups we reduced the power of the analysis by reducing the sample size. Consistently, in some cases we observed trends in the same direction of the main analyses (e.g., SWS % in the subgroup "age" had a p value of 0.06; similarly REM % in the subgroup analyses "sex" and "definition based on subjective criteria only" had a *p* value of 0.06). In spite of the problem with the statistical power, we can still make some speculations for further experimental designs from the results. WASO, when calculated in percentage was found to be not significantly different between groups in the subgroup analysis "age", "definition based on subjective criteria only", and "duration of PI". It could be speculated that an increased time awake may be specifically related with older age. Younger patients with PI, although waking up more frequently than GSC, may be able to get back to sleep quicker than older patients with PI. Moreover, it could be possible that the subjective complaint of patients with PI might be more closely associated with increased SOL, reduced TST, reduced SWS %, or increased NA, than with a longer WASO (%). Finally, further studies should evaluate whether chronic PI is related with adjustment processes both for sleep continuity and sleep architecture variables. The subgroup analysis conducted for the factor "duration of PI", revealed no significant group differences for SOL, TST, SWS %, and REM %.

Sleep diaries and power spectral analysis

Sleep diaries showed similar impairments in patients with PI as observed by PSG, but of increased magnitude: for SEI, the difference between subjective data and PSG data is 12%; for SOL about 20 min; for TST about 50 min; and for WASO (duration in minutes for the PSG data) circa 50 min. Indeed, the discrepancy between the subjective complaint and the PSG change in PI has been previously described. Harvey and Tang[75] recently published a comprehensive review on this phenomenon in PI. One of most likely reasons for this phenomenon seems to be the presence of brief awakenings. Consistent with this, in our analyses patients with PI wake up for an increased number of times compared to GSC.

Furthermore, the use of sophisticated analyses, such as PSA, might be useful to better define the psychobiological profile of PI. Perlis et al.[26] suggested that an increased beta activity in PI, as found in several previous studies, may be indicative of enhanced CNS hyperarousal, which in turn may be the psychophysiological correlate of the misperception of sleep in patients with PI. This theoretical model was further supported by recent experimental studies (for example in the study of Buysse et al.[47] and in a very recent study by Spiegelhalder et al.[34] which was not considered in our work as published after July 2012). However, in our work we were not able to draw conclusions or new hypotheses from the data related to PSA as the studies differed too much in the methodology they applied. It would be interesting to conduct PSA on larger samples, for example, by sharing data between sleep laboratories.

Limitations

A number of limitations of this work have already been described in the discussion of the subgroup analyses. The main problem of the present work is related to the definition of PI which is per se a source of variability. Indeed, although PI is defined as a disorder with nighttime and daytime symptoms, our knowledge about the daytime aspects of the disorder is still limited. There is no consensus regarding which forms of daytime impairment are closely linked with PI and there are no operational definitions of how to measure the daytime component of the disorder. Furthermore, past histories of mental disorders or substance abuse disorders could also have been a source of variability. Indeed, only six studies in our sample specifically reported that patients were interviewed for a history of mental disorders which was an exclusionary criterion (plus 2 studies in which this was partially done, for details see Table 1). Further research should clarify the daytime component of the disorder of insomnia and its close relationship with psychopathology.

Another limitation is that the evaluation of PSG sleep in patients with PI and GSC referred to a single sleep laboratory night (or in some cases to two nights). This might have led to different results compared to more ecological assessments. Additionally, as a result of the pre-scheduled bedtime in some investigations, it is possible that ceiling effects could have veiled some differences. PSG devices that can be used at home and for longer periods of time should thus be promoted. Furthermore, all the studies we have evaluated in our study referred to the Rechtschaffen and Kales[19] criteria. However, in a study by Moser et al.,[76] the authors could show that the new standard criteria published in 2007[20] present differences between sleep parameters to the previous standard criteria. New studies based on the more recent criteria may thus show differences in the PSG profile of patients with PI which have not been documented yet.

An additional point is related to the sex of the participants included in the meta-analysis. It has to be underlined that our sample included about the same number of women and men. As mentioned in the Introduction, PI is more prevalent in women. Thus, it is possible that our results may have been biased by this sex distribution. Further studies are needed to evaluate potential sex differences of sleep in PI patients.

Finally, some studies have been identified to be potential outliers reporting results that are significantly different from those found in the other studies. Of the five studies which we had to exclude from some of the analyses, three studies defined PI based on PSG data, and four predominantly considered a type of PI characterized by sleep maintenance problems. These aspects may explain why these studies presented (in some cases) results that significantly differed from the average of the other studies included in our sample by reporting an even larger difference between the PI and GSC groups.

Conclusions

Consistent with the hyperarousal model,[23,26,27] our meta-analysis showed that patients with PI present a disruption of sleep continuity associated with a moderate, albeit significant reduction of deep sleep and REM sleep. The length of SWS has been shown to correlate positively with cognitive processes, i.e., the consolidation of individual declarative memories (e.g.,[15]). Patients with PI have been shown to display deficits in sleep-related memory consolidation.[77] A loss of slow wave sleep can be associated with the presence of significant psychopathology. For example, in the previous meta-analysis conducted by Benca et al.,[37] a reduction of SWS sleep was found to be present in affective disorders, alcohol dependence, and schizophrenia.

Our results indicate a shortened duration of REM sleep in patients with PI. REM sleep is thought to play a key role for adaptive emotional processes (e.g.,[15]). Insomnia, on the other hand, is associated with an alteration of the emotional system (for a review see[16]). The first theoretical formulation concerning the role of emotion dysregulation in insomnia was proposed by Kales et al.[78] According to this model, the predisposition to internalize psychological conflicts leads to a heightened level of emotional arousal, which in turn provokes physiological hyperarousal and renders the individual unable to sleep, experiencing difficulties in

sleep initiation or in returning to sleep after awakenings during the night. As a result, patients with PI might develop a conditioned fear of sleeplessness that contributes to the maintenance of the disorder. Recent evidence has shown altered psychophysiological responses to emotional stimuli related to sleep, but not to emotional stimuli in general in PI.[79] Considering the findings of our meta-analysis, it can be suggested that a reduction of REM sleep might be a relevant physiological correlate of altered emotional processes in PI. These physiological and psychological alterations seem to be specific for the disorder of insomnia and support the change of conceptualization that will be adopted in the DSM-V. Mood alterations in depression, indeed, are associated with an increased, and not a reduced duration of REM sleep (for a review see Palagini et al.[80]). Abnormal emotional responses in PI could be specifically related to the sleep stimuli as suggested by the model of Kales et al.[78] (patients with PI manifest a specific fear of sleeplessness) and by recent evidence showing that in patients with PI measures of poor sleep are closely associated with sleep-related cognitive hyperarousal and not with general cognitive hyperarousal.[34] With respect to the predictive role of insomnia for depression and psychopathology in general, based on the findings of one study included in our meta-analysis,[50] Riemann et al.[81] have recently suggested that a chronic reduction of REM sleep in some patients with PI might facilitate, at a certain point, a REM sleep rebound. This excessive increase in REM sleep would be the core of an elevated risk to develop depression symptoms in patients with PI.

Considering the sleep profile of PI, it might be possible that this constellation of findings is triggered and maintained primarily by alterations of the arousal system and by increased emotional reactivity specific for sleep processes. These alterations, in the long run, might influence the proper functioning of cognitive and emotional processes in general, by facilitating the development of other psychological problems (see, for example, the functional neuroimaging perspective proposed for depression which suggests the mutual interaction of the three systems of arousal, cognitive functioning and emotional processing[82]).

In clinical practice, the treatment of the symptoms of insomnia in patients with different mental disorders could improve the efficacy of the intervention and should be promoted, as also suggested by recent studies (for a review, see[83]). Moreover, as insomnia often precedes the onset of other clinical conditions (i.e., depression), the diffusion of focused and easily accessible interventions for insomnia in the general population could have a strong impact on mental health.

Practice points

1) PI seems to be associated with a specific sleep profile which is different from the sleep profile of other conditions often comorbid with insomnia, such as major depression;
2) The PSG profile of PI, based on the results of this meta-analysis, is characterized by diminished sleep efficiency, increased sleep onset latency, reduced total sleep time, increased number of awakenings, reduced SWS, reduced REM sleep, and increased wake time after sleep onset;
3) The observed changes in sleep architecture in PI may explain the high comorbidity of insomnia with psychopathology, due to the importance of SWS and REM sleep for cognitive and emotional processes.

Research agenda

1) Variability in the definition of PI should be paid utmost attention to. A deeper knowledge of the daytime symptoms of the disorder may help to identify different PI subtypes with different PSG profiles and clinical characteristics. Moreover, psychiatric histories should be taken in consideration as detailed as possible;
2) The application of sophisticated analyses of PSG recordings (i.e., spectral analysis) should be promoted and homogenized between different sleep laboratories;
3) Sleep architecture changes in SWS and REM sleep in PI might explain its relationship with psychopathology and should be a focus of longitudinal research;
4) Future clinical research should evaluate whether the early treatment of PI can reduce the risk for other psychiatric conditions (i.e., major depression).

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Conflicts of interest

All authors report no competing interests.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2013.04.001.

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